



Ministerie van Volksgezondheid,
Welzijn en Sport

SenterNovem
Agentschap voor duurzaamheid en innovatie

ASAT Innovation Programme

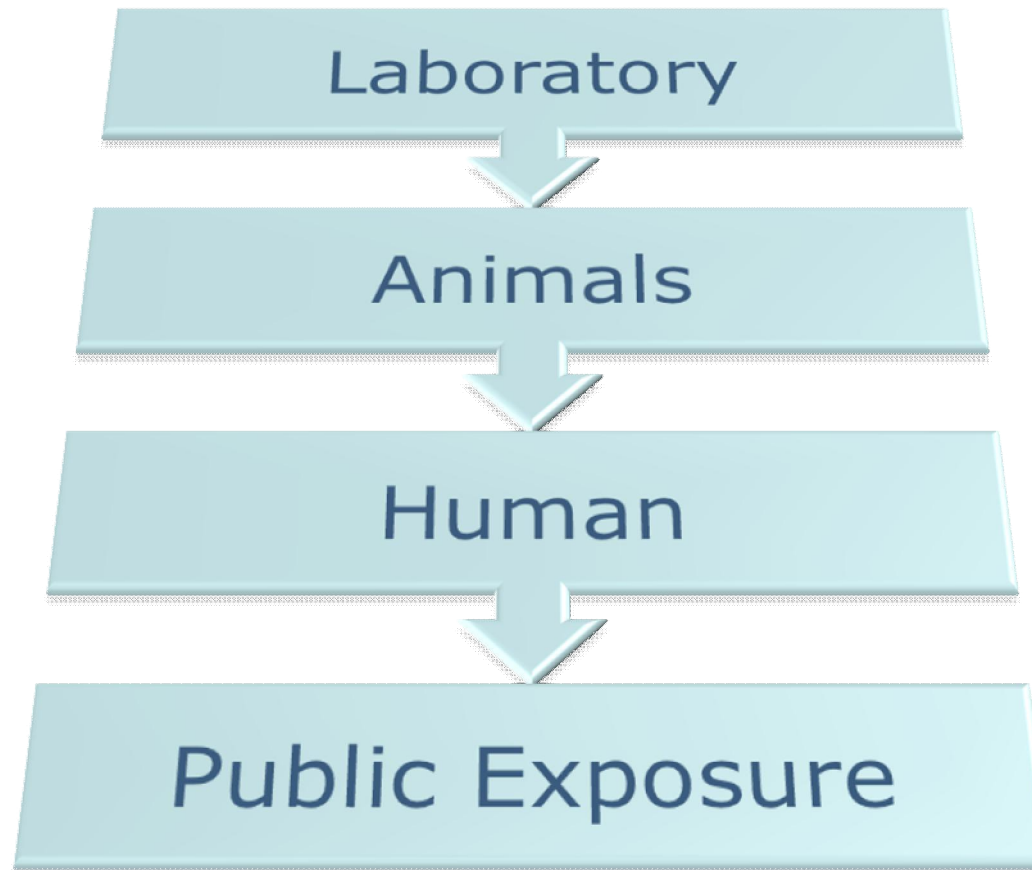
Towards Understanding the Biology of Psychoses

human alternatives for animal testing

Centre for Human Drug Research
Joop van Gerven



Process of Safety Assessment



JvG1

- current drug development process requires testing of new substances in animals, healthy volunteers and patients
- animal testing includes models of human conditions (diseases, side effects, tolerability/safety)
- particularly for complex psychiatric conditions and effects, animal models are of limited value for novel compounds
- in these cases, human disease models may provide more valuable information about effects of drugs and environmental compounds on CNS

Joop van Gerven; 17-11-2008

Psychotic Effects of Therapeutic, Recreational and Environmental Compounds

Environmental Toxins

- Solvents
- Metals
 - mercury
 - lead
 - aluminium
 - thallium
- Others
 - manganese
 - bromides

Recreational Drugs

- Hallucinogens
 - LSD
 - mescaline
 - phencyclidine
- Cannabinoids
- Stimulants
 - amphetamines
 - Cocaine
- Alcohol
- Steroids
- etc

CNS Depressants

- benzodiazepines
- barbiturates
- anticonvulsants
- antihistamines

AntiParkinson Agents

AntiMicrobials

Other Drugs

- anti-inflammatory drugs
- chemotherapy
- immunosuppressants
- digoxin, disulfiram, etc

JvG10
*animal models
are poor
predictors of
human
psychiatric
disorders*

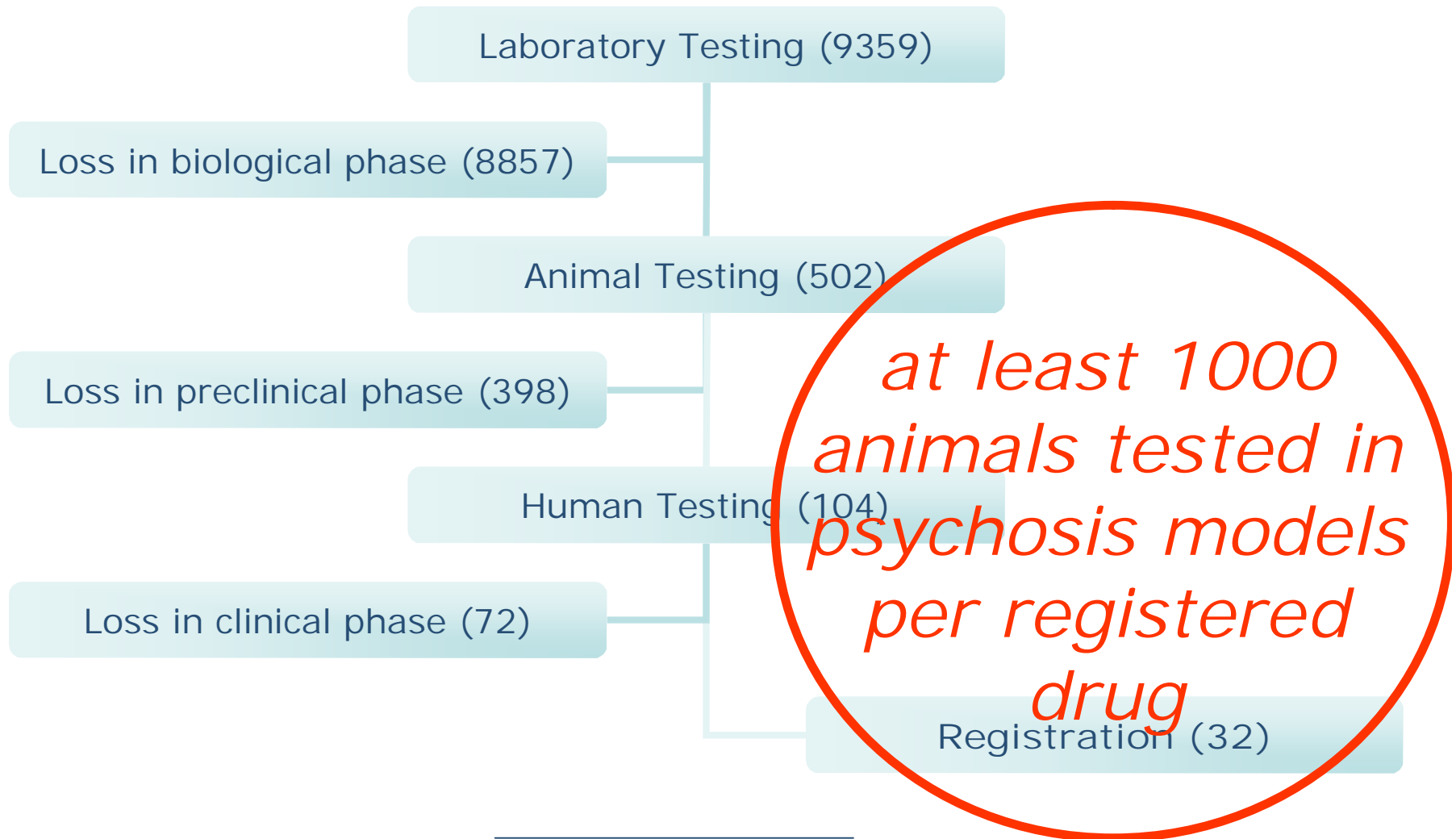
JvG10

Antimicrobials:

- tuberculostatics
- antimalaria agents
- cephalosporins
- sulphonamides

Joop van Gerven; 17-11-2008

Antipsychotic compounds



Animal Models for Schizophrenia

Model agent

- phencyclidine
- ketamine
- amphetamine
- apomorphine
- steroids

Knockout models

- CB1
- COMT
- DBH
- GPRK6
- RGS9
- RIIbeta

Developmental models

- postnatal hippocampal lesion
- isolation rearing
- early maternal deprivation

Effect parameters

- persistent behaviours
- stereotypies
- latent/prepulse inhibition
- sensory gating

JvG4

-large number of animal models indicative of limited understanding of psychosis/schizophrenia
-outcome parameters reflect only some features of psychosis and schizophrenia

Joop van Gerven; 17-11-2008

Pitfalls in animal testing

- Relation of animal models to pathophysiology of psychosis/schizophrenia unclear
- Animals lack most relevant brain circuits
- Animal models do not display typical psychotic symptoms
- Validity is essentially limited to dopamine hypothesis
- Current animal models favour development of (ever more) antidopaminergic antipsychotics
- Limited predictive value for psychotic-like side effects of novel CNS-compounds
- Animal models are performed for novel drugs despite lack of validation

Proposed alternative: human psychosis model

- Healthy, human volunteers
- Administer THC
 - active compound from cannabis
 - affects wide range of CNS networks and neurotransmitter systems
 - well-characterised, highly reproducible challenge
- Measure psychotic-like symptoms
 - clinical rating scale PANSS
- Assess effects of (putative) antipsychotic drug

JvG5

JvG5

...and hence may be more generally representative of wide range of psychotic disorders...

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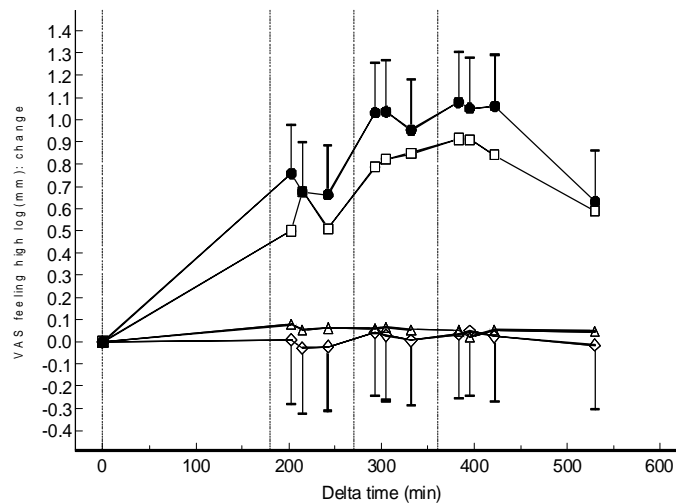
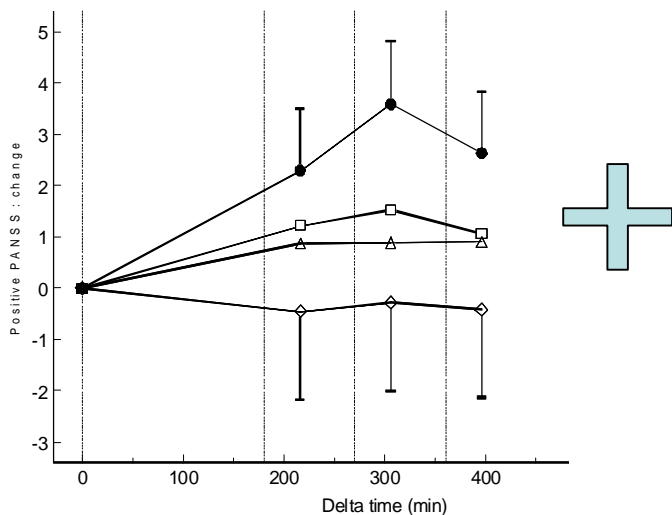
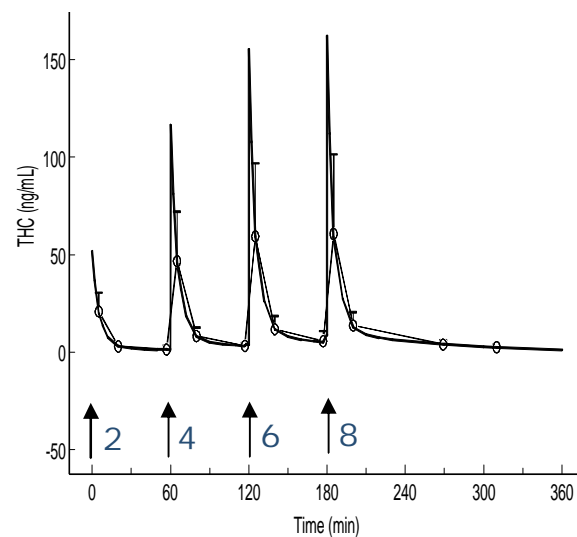
Ethical Considerations

- THC-challenge is safe
 - single low dose of pure THC
 - inhalation of ascending doses controlled by subject
 - experienced (mild) cannabis users
 - adults without psychiatric personal or family history
- Psychotic-like symptoms are mild and transient:
 - disorganised thinking
 - hallucinations
 - delusions
- Full informed consent and ethical approval process (IRB/CCMO/WMO)

Previously tested for prototype neuroleptic (haloperidol)

THC Psychosis Model

Volcano Vaporizer



Implications of Validated Human Psychosis Model(s)

- Reduce added value of animals models of psychosis
- Improved understanding of psychosis/schizophrenia
- Better predictions of psychotic side effects of novel compounds in humans
- Fewer studies with ineffective treatments in vulnerable patient population

Value of ASAT

The ASAT program enables us to:

- Validate this model JvG6
- Investigate the pharmacological basis of psychosis

In the future, this model could:

- Avoid application of useless animal models JvG9
- Provide alternative approach to develop human models for psychiatric/therapeutic effects of other compounds JvG7
- Increase the knowledge and contribute to prevention of psychosis JvG8

JvG6 ...using different antipsychotic drugs and non-specific CNS-depressants...
...which will undoubtedly generate interest from the pharmaceutical industry
Joop van Gerven; 17-11-2008

JvG7 ...such as models for:
-psychotic effects of recreational drugs
-psychiatric side effects of novel CNS-active drugs
-other 'typically human' psychiatric disorders (depression, anxiety)
Joop van Gerven; 17-11-2008

JvG8 -CHDR considers this ASAT project to be important enough to warrant a significant contribution from our organisation
-in 2009, CHDR will devote much of its own research capacity to this study, and in this way contribute about 400000,- in kind to the ASAT program
Joop van Gerven; 17-11-2008

JvG9 ...by offering pharmaceutical industries an informative alternative
Joop van Gerven; 17-11-2008

The ASAT network will start from here

www.ASAT-Initiative.eu